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REPORTS

Preparation and release characteristics of tobramycin-impregnated polymethylmethacrylate beads

JOHN A. GOODELL, ARTHUR B. FLICK, JAMES C. HEBERT, AND JAMES G. HOWE

Abstract: Preparation of tobramycin-impregnated polymethylmethacrylate (PMMA) bone cement beads and release of tobramycin from the beads in vitro and after implantation in a patient are described.

Tobramycin sulfate powder 1.2 g was mixed with Palacos PMMA bone cement 40 g in a custom-made mold to produce 25 beads containing 3.26 mg tobramycin (as the sulfate salt) per bead. Chains of the beads, strung on stainless-steel suture, were sterilized with ethylene oxide. Three single beads were each placed in multiple-electrolyte solution (pH 7.4); the solution was removed and replaced with fresh solution every 24 hours for 28 days. The tobramycin content of each day's solution was determined by fluorescence polarization immunoassay. After day 28, solution was removed weekly for assay until day 84. Tobramycin concentrations were measured in drainage from the surgical wound after six chains of tobramycin-PMMA bone cement beads were implanted in the right acetabulum and femur of a patient whose hip prosthesis had been removed because of infection.

Tobramycin concentrations in the dissolution medium averaged 34.3 μg/mL initially, and 7.5 μg/mL on day 2, gradually decreasing to 0.6 μg/mL on day 28. Release of tobramycin followed a predictable pattern, and variation among samples was small. Over 12 weeks, less than 20% of the theoretically available tobramycin from a single bead was released. Tobramycin concentration in wound drainage was 90.0 μg/mL during the first 24 hours after surgery, while serum tobramycin concentrations were less than 0.5 μg/mL.

Extemporaneously prepared beads of bone cement are effective for delivering high concentrations of tobramycin to an infection site. The potential for toxicity is low because of the small amount of drug released and the extended time over which release occurs.

Index terms: Aminoglycosides; Beads; Carriers; Cements; Concentration; Dissolution; Dosage forms; Implants; Poly(methyl methacrylate); Release; Sustained-action medications; Tobramycin; Tobramycin sulfate; Toxicity

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Since first described by Buchholz and Engelbrecht in 1970,[1] the mixing of antibiotics with polymethylmethacrylate (PMMA) bone cement has been a subject of considerable interest to orthopedic surgeons. In 1977 Buchholz et al.[2] reported the results of the prophylactic use of gentamicin in PMMA bone cement for various total-hip arthroplasty procedures; the infection rate was reduced from 5% in the control group of 1161 patients to 0.8% in the gentamicin group of 2399 patients. Since then, many other studies have confirmed the effectiveness of antibiotic-bone cement mixtures in total-joint anthroplasty procedures for prophylaxis and treatment of deep wound infections.[3-14] Along with numerous clinical studies, various in vitro and in vivo animal studies have shown that selected antibiotics are gradually released from the matrix of PMMA bone cement in clinically useful local concentrations over weeks or months.[15-29] One group of researchers has demonstrated the release of minute amounts of gentamicin from PMMA bone cement for up to five years.[16]

Most pharmacists in the United States are unfamiliar with the mixing of antibiotics with PMMA bone cement, as evidenced by the limited number of references to this in the pharmaceutical litera-

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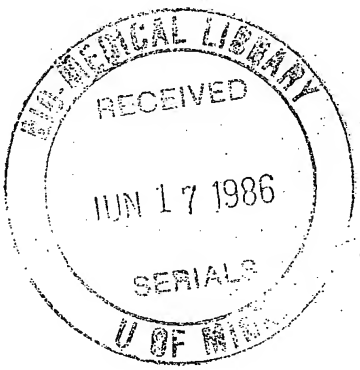

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ture.[9,30,31] Two commercial products consisting of antibiotics mixed with PMMA bone cement are available in Europe: Palacos with Gentamicin and Septopal Chains.[32] Palacos with Gentamicin (Kirby Warrick, United Kingdom) is a premixed PMMA bone cement containing gentamicin powder. Septopal (E. Merck, United Kingdom) is a chain of "beads" made of gentamicin-impregnated PMMA bone cement on a "backbone" of surgical steel wire, resembling a string of pearls.

Septopal Chains are applied locally to infected areas by surgical implantation. As a delivery vehicle for the antibiotic, Septopal has been used extensively in Europe for osteomyelitis, bacterial arthritis, surgical infection, and soft-tissue infections.[33-43] Septopal Chains are usually removed within 10 to 14 days, before granulation tissue prevents their easy percutaneous removal. However, Septopal is well tolerated by tissues,[44] and no adverse effects have been reported from Septopal Chains that have remained implanted permanently.[41]

At the Medical Center Hospital of Vermont, tobramycin sulfate powder has been routinely mixed with PMMA bone cement for selected total-joint arthroplasty revisions. In an effort to apply the same concepts to debrided osseous and soft-tissue infections, antibiotic-PMMA bone cement mixtures were studied further. The result was a tobramycin bead product similar to the Septopal product available in Europe.

A description of the preparation of tobramycin beads, a study of their release characteristics, and a case report of their clinical use are presented.

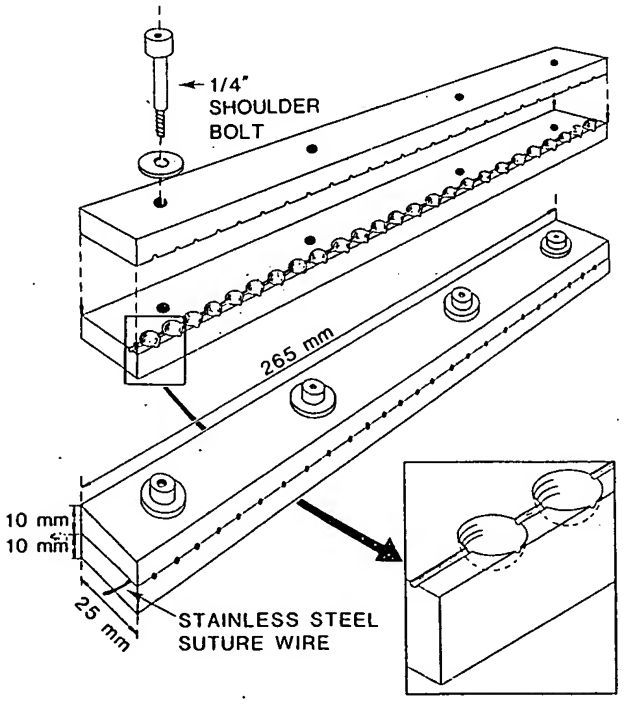
Methods

Preparation of Tobramycin-Bone Cement Beads. Chains of tobramycin beads were prepared using a manufacturing procedure developed, tested, and refined at the Medical Center Hospital of Vermont; no procedures for preparation were found in the pharmaceutical or orthopedic literature. Sterile tobramycin sulfate powder without preservatives or stabilizers,[a] sterile Palacos PMMA bone cement,[b] sterile stainless-steel suture wire,[c] and sterile, custom-made, Teflon-coated molds[d] (Figure 1) were used. Tobramycin powder and PMMA bone cement were mixed in the proportion of 1.2 g tobramycin as the sulfate salt with one 40-g package of PMMA bone cement. The molds were assembled with a multiple-strand, stainless-steel suture wire running through the bead spaces to form the backbone of the chain. The bone cement-tobramycin mixture was then forced into the mold with a 10-mL sterile disposable polypropylene syringe.[e] After time was allowed for the cement to harden (approximately 10 minutes), the molds were opened and the beads removed. Each chain was then individually packaged into sterilizable envelopes[f] and sterilized by ethylene oxide gas (see appendix for complete details of the manufacturing procedure).

Chains of tobramycin beads consisted of 25 large beads or 21 small beads of hardened tobramycin-PMMA bone cement on a backbone of multiple-strand, stainless-steel suture wire. The average weight of individual beads was determined by weighing several chains of beads, subtracting the weight of the wire backbone, and dividing by the number of beads. Antibiotic content was determined by weighing mixed and fully hardened packages of bone cement with and without tobramycin added. Each large bead weighed an average of 160 mg, was 0.63 cm in diameter, and contained a calculated 3.26-mg tobramycin activity per bead. Each small bead weighed an average of 12.8 mg, was 0.32 cm in diameter, and contained a calculated 0.26-mg tobramycin activity per bead.

Dissolution Study. An elution method was used to determine the release characteristics of tobramycin beads prepared from Palacos PMMA bone cement. Studies of drugs other than tobramycin have also used this method,[15,22,26,33] in which an antibiotic-bone cement sample is immersed in an aqueous solution at physiologic temperature and pH and the dissolution medium is changed periodically and assayed. This method promotes maximal release of antibiotic from PMMA bone cement, as opposed to agar-plate diffusion, which has been shown to prolong antibiotic release.[15]

Figure 1. Tobramycin bead mold, manufactured by a machinist from cold rolled steel and covered with a Teflon coating.



A multiple-electrolyte solution[g] with a pH of 7.4 was used as the dissolution medium. Three samples were run, each containing a single large tobramycin bead in 6.0 mL of dissolution medium, and incubated for 24 hours at 37 °C. The dissolution medium was collected and assayed at the end of each 24-hour period. The sides of the tube and its contents were rinsed thoroughly with 5.0 mL of dissolution medium. The rinsing solution was then removed and discarded, and 6.0 mL of dissolution medium was added for the next 24-hour period.

The tobramycin content of the dissolution medium was determined by fluorescence polarization immunoassay.[h] Reproducibility of the analysis was determined daily using controls of 1.0 and 8.0 μg/mL, and the interrun (day-to-day) and intrarun precision was found to have coefficients of variation of less than 4% for the concentrations tested. Sample dilutions were performed when necessary to bring concentrations into the range of the assay standard curve.

On day 28, a second phase of the dissolution studies was begun because the tobramycin concentration of several of the daily samples fell to 0.5 μg/mL, the lower limit of fluorescence polarization assay detection. In phase 2, the partially depleted tobramycin beads from the phase 1 study were subjected to further dissolution testing in which the dissolution medium was changed every seven days instead of daily. Other details remained the same, including the medium, volume, temperature, and rinsing procedure.

Statistical analysis of the raw data was performed using the nonlinear regression program P3R in the BMPD statistical software package.[45] This analysis yields a mathematical equation to explain tobramycin release from the PMMA matrix, indicating the variability and regularity of drug release.

Clinical Study. Clinical results with tobramycin beads were obtained by measuring tobramycin concentrations in wound fluid drainage collected during the postoperative period from a patient who had had tobramycin beads implanted. The patient was a 47-year-old, 65-kg white woman who had had bilateral total hip arthroplasties in 1977. She reported increasing right hip pain that was made worse by walking. Fluid aspirated from the right hip joint contained *Acinetobacter* sensitive to gentamicin and tobramycin. Serum creatinine concentration was 1.0 mg/dL.

Informed consent was obtained from the patient, the acetabular and femoral components of the right total-hip prosthesis were removed surgically, six chains of large tobramycin beads were placed in the right acetabulum and proximal femur (Figure 2), and the wound was closed.

This particular patient was chosen for measurement of tobramycin in wound drainage because of the presence of a Hemovac[i] drainage appliance and adequate quantities of drainage. The Hemovac unit was used to suction excess fluid from the surgical site. Sample dilutions of the wound drainage fluid, which had been in direct contact with the tobramycin beads, were performed to bring concentrations into the range of the fluorescence polarization immunoassay standard curve.

Results

In Vitro Dissolution Study. The in vitro elution study results are summarized in Table 1 and Figure 3. During phase 1, tobramycin concentrations were extremely high initially (average 34.3 μg/mL), de-

Figure 2. Anteroposterior roentgenogram of the pelvis, showing six chains of large tobramycin beads placed in the soft tissues of the patient's right acetabulum and proximal femur.

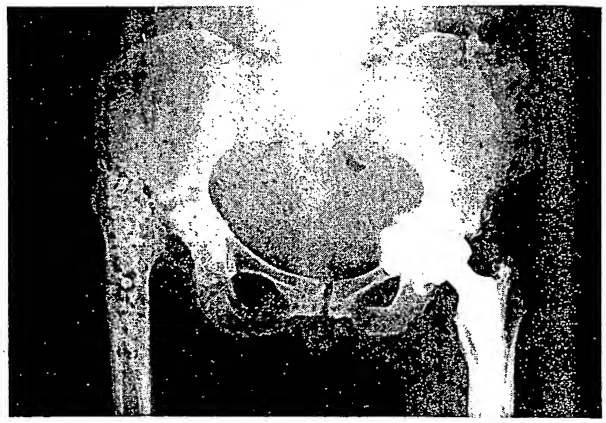


Table 1.
Dissolution Study Results

Day	Tobramycin Concentration (μg/mL) in Dissolution Medium — Sample[a] A	B	C	Mean ± S.D.
Medium Changed Daily (Phase 1)				
1	33.0	32.0	38.0	34.3 ± 2.62
2	7.5	6.5	8.4	7.5 ± 0.78
3	4.1	3.1	4.5	3.9 ± 0.59
4	4.0	2.7	3.7	3.5 ± 0.56
5	4.1	3.0	4.0	3.7 ± 0.50
6	3.3	3.2	3.6	3.4 ± 0.17
7	2.2	2.1	2.6	2.3 ± 0.22
8	2.0	1.8	2.0	1.9 ± 0.09
9	1.8	1.4	1.6	1.6 ± 0.16
14	1.1	1.2	1.2	1.2 ± 0.05
22	0.8	0.8	0.7	0.8 ± 0.05
28	0.5	0.7	0.5	0.6 ± 0.09
Medium Changed Weekly (Phase 2)				
35	3.7	4.3	3.6	3.9 ± 0.31
42	2.3	2.6	2.1	2.3 ± 0.21
49	2.0	2.5	1.9	2.1 ± 0.26
56	1.7	2.0	1.6	1.8 ± 0.17
63	1.2	1.9	1.5	1.5 ± 0.29
70	1.3	1.6	1.2	1.4 ± 0.17
77	0.9	1.3	1.0	1.1 ± 0.17
84	0.8	1.2	0.9	1.0 ± 0.17

[a] Samples A, B, and C were single tobramycin–bone cement beads, each with an initial theoretical tobramycin content of 3.26 mg.

creased rapidly by the second day to 7.5 μg/mL, and then gradually declined to 0.6 μg/mL on the 28th day. Phase 2 studies conducted over the next eight weeks demonstrated a consistent, steadily decreasing release of tobramycin.

The fit of the observed tobramycin concentration data to the computer-generated regression curve was extremely good, producing R^2 values of 0.987 ($p < 0.001$) for phase 1 and 0.904 ($p < 0.001$) for phase 2. This showed that the release of tobramycin from the beads followed a predictable pattern and that the variation between the individual samples was small.

Figure 4 illustrates the percentage of tobramycin released from a large bead. Tobramycin release was much greater in the initial few days after the bead was placed in dissolution medium. The amount of tobramycin released during the 12-week study did not exceed 20% of the total amount theoretically available in the PMMA bone cement matrix.

Clinical Study Results. A tobramycin concentration of 90.0 μg/mL was found in the 70 mL of wound drainage collected over the first 24 hours postoperatively. The drains were removed approximately 18 hours later, and fluid collected up to this time amounted to 20 mL and contained 56.1 μg/mL tobramycin. Serum tobramycin concentrations determined at 3 and 15 hours postoperatively were less than 0.5 μg/mL.

The patient was discharged 21 days after implantation of tobramycin beads; her serum creatinine concentration at this time was 1.1 mg/dL. Outpatient follow-up revealed no clinical sign of postoperative infection.

Figure 3. Mean tobramycin concentrations (± S.D.) during in vitro elution study.

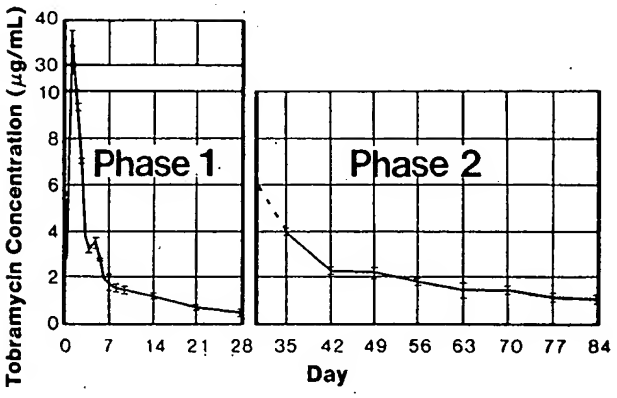
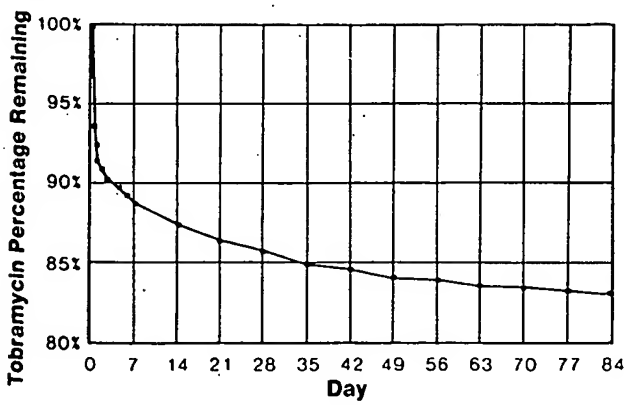


Figure 4. Percentage of tobramycin released from a large bead during 12-week study period.



Discussion

The mixture of many different antibiotics, including aminoglycosides, bacitracin, cephalosporins, clindamycin, colistin, erythromycin, fucidin, penicillins, silver salts, and tetracyclines, with PMMA bone cement has been investigated.[1-8,12,14-27,46-49] Much of the literature has focused on gentamicin because of its high milligram potency against most bacteria, low antigenicity, favorable release characteristics from PMMA bone cement, stability to the exothermic polymerization process of PMMA bone cement, and sustained antimicrobial levels that can be achieved.[1-3,5,6,8,15-18,20-26,46-49] Nephrotoxicity and ototoxicity have not been found as complications of this therapy because of the low serum concentrations obtained.[16,21] In Germany, more than 10,000 patients have been treated with gentamicin mixed in PMMA bone cement in the past decade, and no adverse side effects or bacterial resistance have been reported.[50]

We chose tobramycin sulfate for use in antibiotic beads for the following reasons: gentamicin as a sterile pyrogen-free powder is not available in the United States, our institution has a history of gentamicin-resistant *Pseudomonas* strains, tobramycin has very low allergenicity, and the physicochemical properties of tobramycin and gentamicin are similar.

Characteristics of PMMA Bone Cement. PMMA bone cements consist of two components: a methylmethacrylate-methylacrylate copolymer powder and a methylmethacrylate monomer liquid. Small quantities of stabilizers, catalysts, and inert radiopaque materials are also present. When the liquid and powder components are mixed, an exothermic polymerization reaction occurs, resulting in rapid hardening of the mixture (within 5–10 minutes). Bone cement is used to affix plastic or metal prostheses to living bone in reconstructive arthroplastic surgical procedures. When mixed with PMMA bone cements, antibiotics are generally added to the copolymer powder, then the liquid monomer is added and the bone cement is used in the usual fashion.[4,6,7,10,12,14,15,17-19,22,24,26,27,47,51,52]

The mechanical properties of bone cement after the addition of antibiotics have been investigated by a number of researchers, who concluded that

the addition of small amounts of dry antibiotic powder to PMMA bone cement does not significantly alter the physical characteristics of the cement.[24,25,46-48,51,52] Two of these groups found that aqueous solutions of drug added to PMMA bone cement would interfere with the polymerization process and weaken the cement.[24,46] Moran et al.[51] studied the effect of gentamicin powder 0.5, 1.0, and 2.0 g added to 40-g packages of PMMA bone cement and found a decrease in the shear strength but no change in interface strength between human bone and PMMA bone cement.

Different brands of PMMA bone cement have also been compared for their release characteristics. The Palacos brand of PMMA bone cement was found to release antibiotics in higher concentrations and for longer periods than other PMMA bone cements.[6,24,29] The differences in releasing properties between various brands of PMMA bone cement may be partially explained by morphological differences in the cements as detected by scanning electron microscopy.[53] Palacos was approved for use in the United States in June 1984, and the Medical Center Hospital of Vermont pharmacy began using Palacos for tobramycin beads shortly thereafter.

Mechanism of Drug Release. The mechanism for the release of antimicrobials from PMMA bone cement is controversial. Some investigators have concluded that the drug diffuses through the matrix of the bone cement[6,15,19] and others that it is dissolved from the surface through holes or pores in the cement.[22,24,25] Bayston and Milner[15] offer the best evidence supporting the diffusion theory of antibiotic release. This has important clinical implications for the use of antibiotic-impregnated PMMA bone cement, since it suggests that much more of the antibiotic is available to be released than would be by surface dissolution.

Bayston and Milner[15] also concluded from their in vitro studies that the diffusion of antibiotic through PMMA bone cement is likely to be much slower when the material is surrounded by tissue than when it is immersed in elution fluid; thus, the antibiotic would be released over a longer period of time. This could be caused by the different diffusion conditions and antibiotic concentration gradients present. A smaller concentration gradient would cause the in vivo diffusion process to be prolonged. Therefore, clinically useful concentrations of antibiotic may persist in vivo for longer periods at higher concentrations than the results of in vitro elution studies would indicate. This is consistent with the findings of Wahlig,[44] who reported wound secretion concentrations of gentamicin to be 50–80 μg/mL for at least five days in 10 patients in whom 30–180 Septopal beads were implanted in infected bone cavities. Assays of soft-tissue biopsy specimens in nine of these patients after 30–70 days of implantation showed gentamicin concentrations from 9.1 to 33.5 μg/g of wet tissue.

Use of Tobramycin Beads in the United States. Under FDA regulations, the use of extemporaneously prepared antibiotic beads is a nonapproved indication. Although a physician using these beads is not required to file a notice of clinical investigational exemption for a new drug (IND) or submit data to FDA on the therapeutic results and adverse reactions noted, these steps are often recommended and are sometimes in the best interest of the public.[54] In the absence of an IND, informed consent of the patient, acknowledging the risks and benefits, becomes necessary because of the possibility of adverse effects, which are caused primarily by allergic response to the antibiotic. A severe reaction or anaphylaxis requires the immediate surgical removal of the antibiotic beads.

Authors' Preliminary Studies. Initially, we prepared beads with physical dimensions similar to those of the European Septopal beads. We used Surgical Simplex PMMA bone cement in these beads and then tested them for antibiotic activity using inoculated agar plates. Our experience suggests that gas sterilization using ethylene oxide is superior to sterilization of the beads by autoclaving because the latter causes a potency loss that is evidenced by decreased zones of inhibition on the agar culture plates. The etiology of the potency loss after autoclaving is unknown but may be related to the aqueous solubility of tobramycin.

The amount of tobramycin to be added to a package of bone cement was chosen empirically. The Septopal beads available in Europe contain 4.5 mg gentamicin per bead in a base of Palacos bone cement.[32] We originally decided to use 2.4 g tobramycin with each 40-g package of Surgical Simplex PMMA bone cement, or 1.2 g with each 20-g "half-dose" package. This produced beads containing 6.8 mg tobramycin each. Research done by Elson et al.[6] demonstrated that gentamicin was released about half as well from Surgical Simplex cement as from Palacos bone cement. Thus, we believed that 6.8 mg of tobramycin per bead in Surgical Simplex PMMA bone cement would be comparable to 4.5 mg of gentamicin per bead in Palacos. When Palacos became available, we added 1.2 g tobramycin to each 40-g package of Palacos, producing beads with 3.26 mg tobramycin per bead.

The potential uses of beads in smaller dimensions resulted in the preparation of "minibeads" with a diameter of 3.2 mm for use in small infected areas (see appendix for bead dimensions and specifications). We postulated that the increased surface area might result in a greater antibiotic release for a small area because more minibeads could be packed into the infected cavity. Minibeads were prepared using the same mixture of Palacos and tobramycin, with only the size of the bead changing. Each chain of minibeads consisted of 24 minibeads containing 0.26 mg tobramycin each.

Experience at Authors' Hospital. At the Medical Center Hospital of Vermont, we have used tobramycin beads as an alternative treatment modality for appropriate infections that are difficult to treat or have not responded to conventional therapies. We have treated more than 100 patients using this therapy. In clinical use, extremely high local concentrations are seen in the first few days after surgery, accompanied by subtherapeutic or unmeasurable serum concentrations. In vitro data presented here suggest that if tobramycin beads are left in place, clinically useful tobramycin concentrations will exist for several months after surgery.

Six chains of large tobramycin beads contain a theoretical total of 489 mg of tobramycin. Based on the in vitro dissolution results, one would predict an in vivo antibiotic release of less than 20% (approximately 100 mg) over 12 weeks. The serum concentrations that would be expected with a dose of 100 mg of tobramycin over 12 weeks are consistent with the findings in our case study. In this patient, serum tobramycin concentrations were less than 0.5 μg/mL at 3 and 15 hours after placement of the beads, despite the faster release of antibiotic shown to occur in the first 24 hours. This demonstrates that extremely low and probably nontoxic serum tobramycin concentrations can be expected with the use of tobramycin beads.

Conclusion

Tobramycin beads, prepared extemporaneously in the hospital pharmacy, are an effective delivery system for the local application of tobramycin to an infected area. The use of 1.2 g of tobramycin sulfate powder with a 40-g package of Palacos polymethylmethacrylate bone cement produces beads that release tobramycin in clinically useful concentrations without appearing to affect the structural integrity of the bone cement. Although high local concentrations of tobramycin are found, the potential for toxicity is low because of the small amount of drug actually released and the extended time period over which the release occurs.

[a] Nebcin 1.2-g vial, control number 9LP53A, Dista Products Co., Division of Eli Lilly and Company, Indianapolis, IN, 46285.

[b] Palacos-R radiopaque bone cement 40 g, catalogue number 12-0001, batch number 450/7730, Richards Medical Company, 1450 Brooks Road, Memphis, TN 38116.

[c] Surgical Steel Monofilament B & S 30 Suture Wire, lot SM2DKQ, Ethicon Incorporated, Somerville, NJ 08876.

[d] University of Vermont Instrumentation and Models Facility, 280 East Avenue, Burlington, VT 05401.

[e] 10-mL Plastipak Luer-Slip Tip Syringe, Becton Dickinson, Rutherford, NJ 07070.

[f] Medi-Plus Pouch, Medi-Plus Laboratories, Division of Arvey Corporation, 3500 North Kimball Avenue, Chicago, IL 60618.

[g] Plasmalyte-A Injection Electrolyte Solution (pH 7.4), Travenol Laboratories, lot 2C007P4, Deerfield, IL 60015.

[h] Tobramycin Reagent Pack, TDX In-vitro Test, product no. 9510-20, Abbott Diagnostics Incorporated, North Chicago, IL 60064.

[i] Hemovac drain, large diameter, Zimmer, Warsaw, IN.

[j] Surgical Simplex P radiopaque bone cement, Howmedica Incorporated, Orthopedics Division, 359 Veterans Boulevard, Rutherford, NJ 07070.

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Appendix—Manufacturing Procedure for Tobramycin Beads

Bead Specifications	Large Beads	Small Beads
Diameter	0.63 cm	0.32 cm
Weight	160 mg	12.8 mg
Tobramycin activity/bead	3.26 mg	0.26 mg
No. beads/chain	25	21
Chain length	23.5 cm	15.6 cm
Space between beads	0.32 cm	0.32 cm
Suture wire backbone	#3 3-0 wires	#5 5-0 wires

Materials

1. 10 sterile plastic disposable 10-ml syringes
2. 2 sterile disposable 18 gauge hypodermic needles
3. 1 package Palacos bone cement 40 g
4. 1 vial tobramycin sulfate powder 1.2 g
5. 8 5.25-inch × 10-inch sealable, gas-sterilizable pouches

To be sterilized in advance by autoclave:

6. Mold(s) as needed, large or small
7. 1 stainless-steel teaspoon
8. 2 bone-cement mixing bowls
9. 2 bone-cement mixing spatulas
10. 1 pair stainless-steel bandage scissors
11. 1 10/mL conical glass graduate
12. Stainless-steel wire as needed (three 3-0 wires wound together for each large bead chain; five 5-0 wires wound together for two small bead chains)

Preparation

1. Perform all operations under laminar-airflow hood, using strict aseptic technique. A vertical laminar-airflow hood with outside exhaust (class II, type B) is preferred because of the highly volatile and unpleasant vapor from the bone-cement liquid.
2. Each package of bone cement and vial of tobramycin make eight portions of bone cement–tobramycin mixture, and each portion is sufficient for the preparation of one chain of large beads or four chains of small beads. The large bead molds make one large chain of beads and the small bead molds make two small chains of beads. To conserve materials, it is advantageous to have two small bead molds so that one portion of bone cement is completely used.
3. Aseptically arrange the needed materials and equipment.

4. Draw up methylmethacrylate monomer liquid 10 mL into each of two 10-mL syringes with 18 gauge needle attached.
5. Add the methylmethacrylate–methylacrylate copolymer powder and tobramycin powder to a bone-cement mixing bowl. Mix well by covering the bowl with a second mixing bowl and shaking for at least one minute, similar to the way a cocktail shaker is used.
6. Assemble the bead mold and wire so that they are ready to be used, and set them aside. Remove the plunger from an empty 10-mL syringe and set both pieces aside, ready for use.
7. Steps 8–10 require the mixing of bone cement, transferring the mixture to a syringe, and squeezing the mixture into a mold. The cement begins to harden within five minutes, requiring these steps to be performed in an expeditious manner.
8. Measure 7.0 mL of bone-cement powder-tobramycin mixture into a conical graduate. Place 2.5 mL of the bone-cement liquid into an empty bone-cement mixing bowl. Add the bone-cement powder to the 2.5 mL bone-cement liquid, and mix well for approximately 30 seconds using a mixing spatula.
9. When a smooth mixture is obtained, place it into a 10-mL plastic syringe (through the syringe barrel with the plunger removed). Replace the syringe plunger. Expel air from the syringe while holding the syringe tip upward.
10. Place the tip of the syringe against the opening on the mold for the first bead, and squeeze the plunger until the bead space is filled. Repeat this step until all the bead spaces have been filled. Using a bone-cement mixing spatula, scrape excess cement from the top of the mold.
11. Set the mold aside to allow the cement to harden. Remove any remaining cement from the syringe and use it to determine the progress of the cement inside the mold (when the extra cement is hardened, the mold is ready to be opened).
12. When ready, open the mold and remove the beads. Scrape excess cement that formed in the mold joints from the beads using a bone-cement mixing spatula. Cut away excess wire from either end of the tobramycin bead chain using the sterile stainless-steel scissors, leaving approximately 5 cm wire on each end. If making small bead chains, cut the two chains apart.
13. Clean the used mixing bowl, and repeat steps 5 through 12 until the bone-cement liquid is used up. If done properly, there should be little or no bone-cement powder left at the end of the procedure.
14. Place each chain of tobramycin beads into a sealable, sterilizable envelope. Label, with a six-month expiration.
15. Seal the envelopes and sterilize by ethylene oxide gas. *Do not autoclave* (autoclaving will cause a potency loss).

Effect of pharmacists' clinical interventions on nonformulary drug use

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Abstract: The effect on drug costs of pharmacists' interventions in reducing the use of nonformulary medications was studied in a private teaching hospital.

During a four-month period, nonformulary medication request forms and pharmacist consultation logs were reviewed to determine physicians' actions taken on requests for nonformulary medications. Cost avoidance of interventions (nonformulary medication cost minus formulary medication cost) and the cost of pharmacist time for the interventions were determined.

The pharmacist was able to contact the physician in 388 of 394 instances in which the use of a nonformulary medication was considered. Of 230 recommendations by pharmacists to change a nonformulary drug order to one for a formulary alternative, 64.8% (149) were accepted by physicians. Of pharmacists' recommendations that were accepted, 75.8% (113/149) were from decentralized areas, which was a significantly higher acceptance rate than that for the centralized areas (24.7% or 36/149). Cost avoidance resulting from acceptance of pharmacists' recommendations during the four-month study was $2,645, or $13,573 per year; this was more than the cost of pharmacist time required to perform interventions.

Pharmacist interventions to decrease use of nonformulary drugs can be cost-effective and appear to be more successful in decentralized pharmacy service areas than in areas served by a central pharmacy.

Index terms: Clinical pharmacy; Control; Costs; Drug use; Economics; Formularies; Hospitals; Pharmaceutical services; Pharmacists, hospital; Pharmacy, institutional, hospital; Physicians; Prescribing

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Because of the implementation of the prospective-pricing system as part of the Social Security Amendments of 1983, numerous incentives exist for hospitals to limit the costs associated with providing patient care, particularly drug costs.[1-3] Drugs and drug-related costs constitute a substan-

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